FAX

Date 13 October 1999

Number of pages including cover sheet 2

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JANE AXELRAD

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FROM: JORGE R. BARRIO

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CC:

REMARKS: ☐ Urgent ☐ For your review ☐ Reply ASAP ☐ Please Comment

Dear Jane:

We thought that the section on profit-non-profit entities was not sufficiently clear in our letter of October 11. The enclosed letter (October 13) clarifies our views. We think that further discussions on this will be very helpful.

Regards

Jorge

980-0266

C6

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October 13, 1999

Ms. Jane Axelrad, J.D.
Associate Director of Policy
Center for Drugs Evaluation and Research
Food and Drug Administration
5600 Fishers 'Lane
Rockville, MD 20857

Dear Ms. Axelrad:

As a point of clarification to our letter of the 11th of October 1999, we would like to stress two important points:

(i) The intent of our first general comment was to delineate the various alternatives that we felt should be available for manufacturing PET drugs and to clarify the boundaries of FDA jurisdiction from the activities that would remain within the practice of pharmacy and medicine. We believe that FDA regulatory jurisdiction over a manufactured batch of a radiopharmaceutical (whether that is a manufactured unit dose, several unit doses, or multi dose vial) should end with the QC release of the final product. Dispensing and administration to a patient always takes place under the regulations governing the practice of pharmacy or medicine.

(ii) Specifically, the issues regarding the delineation of the manufacturing process and the practice of pharmacy and medicine should not have any connection with a definition of profit/non-profit entities. The latter is a complex issue and, it is our understanding, has been deferred by the FDA. We look forward to discussing this definition with the FDA in the very near future.

Sincerely,

Jorge R. Barrio, Ph.D.
Chairman, Radiopharmaceutical Committee

Jennifer Keppler
Executive Director, ICP

FAX

Date 10/11/99

Number of pages including cover sheet 6

TO:

Jane Axelrod

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REMARKS: ☐ Urgent ☑ For your review ☐ Reply ASAP ☐ Please Comment

Dear Jane,

Thank you for the opportunity to review your CGMPs. Our comments are enclosed.

Regards

Jorge

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October 11, 1999

Ms. Jane Axelrad, J.D.
Associate Director of Policy
Center for Drugs Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20847

Dear Ms. Axelrad:

We appreciate the opportunity to have an open discussion with you and FDA staff about Current Good Manufacturing Practices (CGMPs) proposed by the FDA for PET radiopharmaceuticals. Outlined below are the PET Radiopharmaceutical Committee's comments on the preliminary draft of CGMPs proposed by the FDA in the public meeting of September 28th 1999.

General Comments;

1. **Compounding, practice of pharmacy and medicine,** Any reference to nomenclature or activities traditionally associated with the practice of pharmacy and medicine should be removed and/or clarified. We have tried to outline in our comments below how this can be done.

   The ability of a manufacturer to produce either multi-dose vials or [not-patient specific] single dose syringes should be maintain4 In either case, these can be transferred to either a pharmacy for patient-specific dispensing or to a duly licensed physician for use in his practice.

   In academic/non-commercial sites (not for profit), the same person/group that is manufacturing the drug product may also, under the order of a physician, draw and dispense a patient specific-dose. In a commercial environment (for profit), a site may sell/distribute a vial to a licensed pharmacy, who on tho order of a physician may draw and dispense a patient-specific unit dose, as per the practice of pharmacy. Alternatively, a site may choose to manufacture [not-patient-specific] single-dose syringes or vials that would go to a licensed physician for use. We recommend inclusion of language for a clear ddimitation ol FDA jurisdiction.

2. **Validation requirements** for USP methods as well as methods that have been in use for the many years in the preparation of well-established PET drug products should be minimized in the guidance. The committee believes that if the FDA implements the suggested validation guidelines, a considerable amount of unnecessary additional work will be required of each PET facility in order to produce a final product of the same quality as is being produced currently. We also strongly believe that retrospective, repeated end product validation is an appropriate mechanism for validation of many of the methods used in preparation of well-established agents. To address areas of concern, the Committee will evaluate putting together a centralized DMF addressing the validation of analytical quality control methods for reference by the PET community. The committee would appreciate additional recommendations from FDA staff regarding other centralized efforts that may facilitate compliance with the proposed validation requirements by individual PET centers.

3: **Teat Equipment Failures.** Wc respectfully request that the FDA give consideration to the development of guidelines that will permit the release of PET drugs in the absence of an analytical test result due to respective equipment breakdown. The release of final drug product could be based on (1) verification that monitoring of in-process controls has demonstrated that all parameters are within a normal range; and (2) historical data indicating that the parameter that could not be tested consistently is found within specifications. Tn the absence of such a guideline, PET centers will be required to duplicate, all analytical equipment at a considerable expense or delay diagnosis and treatment of patients being seen at a center.

We also suggest the following specific comments in the proposed draft CGMP document:

Section 212.1 Definitions

1. The following definition is added for "ACTIVE INGREDIENT".
Active ingredient: Any component that is intended to Provide a direct effect in the diagnosis or evaluation of a disease or condition.

2. The definition for "compounded PET drug" should be removed. We realize that the term compounded PET drug is defined as such in FDAMA, however, its inclusion here without a concordant definition for manufactured PET drug is confusing. If the intent of its inclusion is to clarify that the regulations are applicable to both compounded PET drug Products as well as manufactured PET drug products, we recommend that this be addressed in Section 212.2. Also, the current definition of "compounded PET drug" implies that the CGMPs are applicable to PET drugs used for research, teaching, or quality control. If this ddinition remains, references to "research, teaching, and quality control" should be deleted.

3. The definition for theoretical yield needs to be removed and or clarified to include a range. This will also necessitate a change in the definition of "percentage of theoretical yield".

4. The definition for "receiving facility" should be modified as follows:
Receiving facility means any **hospital, imaging facility**, pharmacy, physician office or other entity that accepts a PET drug for subsequent dispensing for human use.

Section 212.40—Control of Components, Containers and Closures

1. **In section (c) (1) and (2), the requirement for performing specific identity tests should be waived if a certificate of analysis is available and the component is purchased** from a **reliable manufacturer. Reliability, as suggested in (2) can** be defined in the guidance document, but could in part be based on having a track record use of the component without **synthesis and/or component failures.**

Verification, without use of a specific identity test is **adequate, given** a batch **size of one** and final drug product **testing. In traditional manufacturing** practices, specific identity **testing is** grounded economically, because **of batch size** and the resultant cost in supplies and delays if the component **were** to fail. Such specific identity **tests** should not be required and, for the **single-employee** PET site, would represent an **unnecessary** burden.

Section 212.50—Production and Process Controls

1. **In (c) (1),** it is not possible to prospectively define the strength of a PET drug, therefore **should be modified to allow a range of acceptable strength.**

2. In (c) (2), references to "dosage unit" are inappropriate. The requirement should be stated in terms of a "batch".

3. *In* (c) (5), reference to theoretical **yield** should be **replaced** or clarified to permit a **range.**

4. **In** (d). the 5th **line should** be modified to allow **weights** *or measures* of components to be **used**.

5. In (e), the reference to "dispensing" should be removed and replaced with the word packaging.

6. **As** discussed in (h), delete **the** requirement for maintaining a "reserve" sample for 30 days.

Section **212.60—Laboratory Controls**

1. **In section** (d), prepared solutions should also be labeled with the date of expiration.

2. In section (g) (2), during our discussion on September 28th, it was clarified that the reference to maintaining the weight and/or measure of the sample used in the test was necessary only as a part of the written "procedure" not in the record itself of each test. Therefore, this sentence should be reworded as follows:

(2) A description of each method used in the testing of the sample, which shall include a record of all the calculations that are to be used in connection with each test, and a specification of the approximate weight or measure of the sample to bc tested.

Section 212.70—Finished Drug Product **Controls and Acceptance Criteria**

1. In section (b), sterility tests should bc started within 24 hours of release, not immediately, in the interest of keeping radiation exposures as low as reasonably achievable.

Also in section (b), delete the statement "In addition, the doctor who wrote the prescription or the PET drug must be notified."

2. In Section (d) (2) – delete "associated laboratory data".

Section 212.80

1. In section (b), change to "the date and time of calibration".

Section 212.90—Distribution

1. Section (a), change "to ensure that only those products that are approved for release are used" to "to ensure only those products that arc approved for release are distributed to the receiving facility."

2. Also in section (a), delete "that prescriptions are reviewed to ensure that they arc properly filled".

3. Section (b) (1) should be modified to include the name of the receiving facility or physician.

4. Section (b) (3), the words "patient's prescription, if applicable, or" should bc deleted.

One of the most challenging things we face is trying to convey the intent of what is required into words that will be lacer interpreted properly. The PET community would like to develop a mechanism to participate in the 483 review process, to facilitate implementation of these regulations. In this way. the dialogue that has proven so productive over the past two years can he extended through implementation.

Thank you again for the opportunity to allow us to assist you and your staff in the formulation of these important regulations. We would like to offer our continued assistance in refining and developing the subsequent guidance for their interpretation. Since several members of your PET team will be in Vancouver on October 26th, 1999 for the FDA-PET workshop, we request the opportunity to meet with you and your staff following the workshop to continue these discussions.

Please feel free to contact us if you have any questions or specific comments.

Respectfully,

Jorge R. Barrio, Ph.D.
Chairman, Radiopharmaceutical Committee

Jennifer Keppler
Executive Director, ICP